Oxidative C–C bond formation in heterocyclic chemistry

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Dedicated to Professors Larry Overman and Alois Fürtsner for their seminal contributions to heterocyclic chemistry

Abstract
There are remarkable advantages to be gained in terms of efficiency (lack of protecting groups, halogens, disposable functional groups), practicality (extremely concise sequences), stereocontrol (complete diastereoselectivity often observed), and conservation of oxidation state (oxidation state increases linearly in a synthesis by using innate functionality) when oxidative C–C bond formation is employed strategically. This account briefly highlights some of our work in this interesting area over the past two years, including total syntheses of the hapalindoles, fischerindoles, ketorolac, avrainvillamide, and stephacidins.

Keywords: Total synthesis, stephacidin, hapalindole, fischerindole, ketorolac, C-C bond formation, natural products

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1. Introduction

In the arena of total synthesis the practitioner is often faced with the exciting challenge of expanding current methodology and developing new approaches to recurring structural motifs found in their targets.\(^1\) Natural products provide a solid foundation for discovery and routinely chart a course to the invention of useful new chemistry.\(^2\) The end result of such endeavors, aside from a clearer understanding of organic chemistry, is the discovery and development of new synthetic tools\(^3\) and access to potential pharmaceutical leads\(^4\) which have extensive applications in the fields of biology and medicine. In fact, the greatest cures to the ailments afflicting humanity have come from or been inspired by natural products.\(^5\)

Although indole alkaloids have been the subject of synthetic efforts for well over a century, those who continue to pursue these targets continue to discover new, useful means of accomplishing transformations that have proven to be inefficient, impractical, or even impossible with existing methods.\(^6\)

Two classes of indole containing natural products captured our attention due to their exciting bioactivity and startling complexity (Figure 1). The first was the hapalindole family of natural products,\(^7\) which include the hapalindolets, fischerindolets, welwitindolinones, and ambiguines, which contain amazingly compact and highly functionalized polycyclic structures. The more than 40 members of this family, isolated by Richard Moore in collaboration with Eli Lilly, were shown to be active antibacterial, antialgal, and anticancer agents. The second class was the stephacidins,\(^8\) composed of stephacidin A, avrainvillamide (CJ-17,665), and stephacidin B which “represents one of the most structurally complex and novel alkaloids occurring in nature.”\(^9\) This family exhibits potent *in vitro* cytotoxic activity against a variety of human tumor cell lines.

Our approach to the invention of chemistry to synthesize the natural products presented in this review was driven by the belief that excessive oxidation state manipulations should be avoided where possible in a total synthesis. There is much new chemistry to be discovered by exploiting the innate reactivity of molecules during coupling processes.\(^10\) This review broadly explores the success that has been garnered in the realm of oxidative C–C bond forming processes through the synthesis of these two families of natural products, which hold considerable potential for heterocyclic chemistry.
**Figure 1.** Oxidative C-C bond formation in synthesis: Brief graphical summary of progress
2. Hapalindoles and Fischerindoles

Our retrosynthetic analysis of hapalindole Q was born after asking the following question: “Can the intrinsic reactivities (and oxidation states) of indole and carvone be used to our advantage?” In the literature, it has been hypothesized that oxidative enolate coupling reactions proceed via oxidation of the enolate to the corresponding α-radical, which simply dimerizes with another radical to form the 1,4-diketone. We imagined that if the oxidation of carvone and indole anions were to occur simultaneously in the same pot, then perhaps they would couple to provide the coveted indole-carvone hybrid 7 (Figure 2). This approach would eliminate unnecessary oxidation state manipulations and even protecting groups for the indole N–H. In fact, this approach was contingent on the existence of a free indole N–H! Several factors could contribute to the demise of this lofty plan: (1) the oxidation potentials of the two substrates might be too different to allow for heterodimerization, (2) the indole might couple at nitrogen rather than carbon, (3) most oxidative enolate couplings demonstrate a complete lack of diastereoselectivity, and (4) the heterodimerization of two different types of carbonyl compounds or a metalloenamine was unprecedented.

To our delight, when the reaction was attempted, it furnished the desired indole-carvone hybrid 7 as a single diastereomer, albeit in low yield. This initial result was encouraging and we set out to optimize the yield of this remarkable transformation to synthetically useful levels. It should be noted that this first skirmish was not clean and generated at least ten to fifteen compounds, from which 7 was obtained. After a series of experiments, some of which are summarized in Table 1, we were able to increase the yield of this reaction to 53% isolated yield (70% based on recovered sm). It should also be noted that this coupling reaction is quite clean. Only carvone, indole, and product are observed, along with a small amount of carvone dimer. In addition, a commercially available and inexpensive copper(II) source [copper(II)]2-

Figure 2. Design of the coupling of indoles with carbonyl compounds. The first mechanistic blueprint.
ethylhexanoate] is used as oxidant. As this reaction is amenable to scale-up (>100 mmol scale), it enabled a gram-scale entry into the hapalindole and fischerindole alkaloid families via an enantioselective route devoid of protecting groups. Surprisingly, only substoichiometric amounts of oxidant relative to the coupling partners are necessary to carry out the reaction.

**Table 1.** Selected results from the optimization of the indole-carvone coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i (1.0 eq), c (3.0 eq), LDA (4.0 eq), Fe (4.0 eq), -78 to 23 °C</td>
<td>ca 15</td>
</tr>
<tr>
<td>2</td>
<td>i (1.0 eq), c (3.0 eq), LDA (4.0 eq), Cu (4.0 eq), -78 to 23 °C</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>i (1.0 eq), c (1.0 eq), LDA (2.0 eq), Cu (2.0 eq), -78 to 0 °C</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>i (3.0 eq), c (1.0 eq), LDA (4.0 eq), Cu (4.0 eq), -78 to 0 °C</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>i (1.0 eq), c (1.0 eq), LDA (3.0 eq), Cu (3.0 eq), -78 to 0 °C</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>i (1.0 eq), c (1.0 eq), LHMDS (3.0 eq), Cu (3.0 eq), -78 °C</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>i (1.0 eq), c (1.0 eq), LHMDS (3.0 eq), Cu (1.5 eq), -78 °C</td>
<td>53 (70) b</td>
</tr>
</tbody>
</table>

a isolated yield chromatography; b yield based on recovered sm

Once this key coupling reaction was optimized, only two steps remained to complete the total synthesis of hapalindole Q (2, Figure 3). The first task was to install the vinyl-containing quaternary center, a feature common to this class of natural products. This was accomplished in a single operation that began with deprotonation of the indole N–H in 7, which served two purposes: (1) to prevent internal quenching of the enolate formed upon conjugate addition of hydride from L-selectride (which was faster than deprotonation of the N–H) and (2) to protect the α-carbon from epimerization. After deprotonation with LiHMDS, L-Selectride was added, followed by quenching with acetaldehyde. Dehydration of the resulting alcohol with Martin’s sulfurane provided the desired indole 8 with nearly perfect diastereoccontrol (d.r. > 20:1). The last step required the diastereoselective conversion of the ketone moiety to an isothiocyanate group. Arrival at 8 actually represented a formal synthesis of hapalindole Q since it intercepted Albizati’s synthesis. Using Albizati’s conditions we were indeed able to arrive at the desired amine 9, however it required a reaction time of 7 days and gave a 3:1 mixture of diastereomers. Interestingly, if the reaction was performed under microwave irradiation, the same yield of amine 9 was obtained after two minutes (150 °C), with an increased diastereomeric ratio of 6:1. This represents a unique instance of an increase in observed diastereoselectivity with a microwave vis-à-vis conventional thermal conditions. Formation of the isothiocyanate from the amine with thiocarbonyl diimidazole then provided hapalindole Q (2) in good yield (Figure 3).
Figure 3. Concise, enantioselective, protecting group-free total syntheses of hapalindole Q (2) and fischerindole U (1).

In order to chart a course to the fischerindole class of natural products, in particular fischerindole U isonitrile 1, we needed to effect cationic ring closure of the isopropenyl group onto the indole. Precedent for this type of closure comes from elegant work published by both the isolation chemists$^{16}$ and the Fukuyama$^{17}$ group. Thus, treatment of 8 with triflic acid effected the desired closure to tetracycle 10, followed by standard reductive amination (d.r. = 10:1) and isothiocyanate formation to provide the first synthetic fischerindole. The synthesis also served to establish the absolute configuration of this natural product. Further work on this family of natural products have resulted in the completed total synthesis of fischerindole I (5) and fischerindole G (6, Figure 4).

Figure 4. Total synthesis of fischerindole I (5) and fischerindole G (6).

3. Direct Coupling of Indoles and Pyrroles with Carbonyl Compounds

The direct coupling of indoles with carbonyl compounds bridged an important gap in indole chemistry. Prior to this work, only one example of an “α-indolylation” existed in the literature.$^{15}$
As shown in Figure 5, the synthesis of adduct 11b required protecting groups, prefunctionalization, stoichiometric amounts of a toxic metal (Sn), use of an expensive palladium catalyst, and proceeded in a modest yield of 34% (over 4 steps) as a 5:1 mixture of diastereomers (51% yield for the key palladium-mediated coupling). Two-thirds of the molecular weight of indole 11a is extraneous, present only to allow coupling to occur. Although the pioneering efforts of Buchwald and Hartwig have served to catapult the utility of palladium catalyzed α-arylation technology to awe-inspiring levels, α-hetero arylation with indoles and pyrroles has yet to be reported. This is an unfortunate omission since indoles and pyrroles are the most widespread heterocycles in nature and are found in numerous medicines. The importance of these heterocycles in drug discovery and human health cannot be overemphasized.

Figure 5. The sole example of “α-indolylation” from the literature.

By employing the same conditions which were successful for the union of carvone and indole we were able to expeditiously access a number of indoles which were previously unobtainable by direct means as shown in Table 2. Simple ketones, esters, and amides work well, and the reaction can be used to form quaternary centers with complete diastereocontrol (12). Compounds with unprotected functionality (13) can also be coupled, requiring only an extra equivalent of LiHMDS. In addition, the reaction can be performed using chiral auxiliaries to give good levels of stereocontrol. Importantly, a wide range of functionality and substitution patterns is tolerated on the indole ring (Table 2).

Just as there were no methods for “α-indolylation” of carbonyl compounds at the outset of this work, there were no methods for the “α-pyrrolylation.” One could assume that Buchwald-Hartwig type chemistry could be employed, but this has yet to be reported. Even so, such a reaction would require a protecting group on the pyrrole nitrogen along with a suitably positioned halogen atom.
Table 2. Previously impossible or difficult to access pyrroles and indoles are now easily prepared

<table>
<thead>
<tr>
<th>Pyrrole or Indole (Yield %)a</th>
<th>Pyrrole or Indole (Yield %)a</th>
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<tr>
<td><img src="image" alt="Pyrrole or Indole (Yield %)a" /></td>
<td><img src="image" alt="Pyrrole or Indole (Yield %)a" /></td>
</tr>
</tbody>
</table>

aisolated yield chromatography; byield based on recovered starting material

There are several potential problems that could ruin our hopes for a pyrrole-carbonyl coupling: (1) pyrroles are much less stable than indoles and problems could be encountered in the single electron oxidation or purification steps, (2) pyrrole might couple at nitrogen, C–2, or C–3, and (3) pyrroles are known to polymerize under radical conditions. Despite these concerns, the reaction was performed using the optimized conditions from the indole coupling, which gave, to our delight, coupled products with a pyrrole attached at C–2 to the α-carbon of a carbonyl compound. X-ray analysis (See Table 2) of pyrrole 14 confirmed that the pyrrole was indeed linked at C–2. This result is in perfect agreement with the intrinsic electronic preferences of indoles and pyrroles. Indoles tend to react at C–3 since that is the location of greatest nucleophilicity, while pyrroles tend to react at C–2 for the same reason. After a slight modification of the indole coupling conditions, efficient pyrrole coupling was attained, and a study was undertaken to determine the scope of this reaction (Table 2). Thus, pyrroles have been found to be amenable to coupling with ketones, esters, amides, lactones, and lactams. In addition, stereoselective couplings can be performed using an appropriate chiral auxiliary, quaternary pyrrole-containing centers are accessible, and a wide range of electron-rich
substitution patterns is tolerated on the pyrrole ring. In general, care must be exercised in handling these compounds, since pyrroles are rather acid sensitive and decompose gradually after workup or during chromatographic separation. This property factored into some of the lower yields observed. On the other hand, the high reactivity of pyrroles is fortuitous since they can be converted to a multitude of other important heterocycles such as pyrrolidines, pyrrolidinones, and pyridines.19

4. Ketorolac

As shown in Figure 6, the pyrrole acetic acid scaffold is found in the widely marketed pharmaceutical agents tolmetin and ketorolac (3) and the previously marketed agent zomepirac. Ketorolac (3, Toradol™ and Acular™) is currently administered as a racemic mixture despite the knowledge that the (S)-antipode is 100 times more active than the (R)-antipode and has fewer side effects.21

Figure 6. Pyrrole acetic acid based pharmaceutical agents.

Our aim was to explore the direct coupling of pyrroles and carbonyl compounds in an intramolecular setting by targeting (S)-ketorolac (3) for synthesis. It was not our intention to improve upon the extremely efficient and practical five-step Syntex route (ca. 45% yield from pyrrole, racemic).22 Rather, 3 served as an ideal proving ground for the versatility of the current method, which led to some interesting mechanistic insights (vide infra). Figure 7 illustrates the final pathway to 3, which is concise, enantioselective,23 and protecting group free.

The synthesis (Figure 7) commences with pyrrole acid 15, available from the nearly quantitative union of pyrrole with butyrolactone on multi-gram scale.24 The stage was set for an intramolecular pyrrole-carbonyl coupling after installing the chiral auxiliary to afford 17.25 In the event, we were unable to achieve the oxidative annulation of 17 with many standard oxidants (CuII, FeIII, AgI, AgII, TiIV, MnIII, CeIII). After considerable exploration, ferrocenium hexafluorophosphate (18, a practical, recyclable, and commercially available oxidant),26 was found to elicit the cyclization of 17 to 19 in 65% yield (based on recovered sm, determined by 1H NMR) as a 4.5:1 mixture of diastereomers. The actual yield of 19 was ca. 35%, however, since 19 was quite sensitive to air and moisture the crude reaction mixture containing 17, 19 and ferrocene was carried forward without purification (BzCl, 70 °C; remaining 17 and ferrocene easily separable).27 Hydrolysis of the resulting benzoyleated pyrrole using tetrabutylammonium hydroperoxide28 furnished (S)-ketorolac (3, 90% ee determined by chiral HPLC, 25% isolated
yield over 3 steps) along with recovered chiral auxiliary. From the vantage point of synthetic
design, certain details are worth noting: (1) the oxidation state of 15 is conserved (reduction,
de carboxylation, and halogenation processes avoided),\(^{29}\) (2) protecting groups are absent; (3)
decent stereocontrol is observed in the ring closure despite the readily enolizable\(^ {23}\) nature of the
newly formed stereocenter; and (4) overall brevity of the sequence (ca. 25% overall unoptimized
yield from pyrrole in four operations).\(^ {30}\)

Figure 7. Short, enantioselective, protecting group-free synthesis of (S)-ketorolac (3).

5. Proposed Mechanism of the Direct Coupling Reaction

There are significant mechanistic issues that arise from the interesting observation that only the
Fe(III)-based oxidant 18 could elicit the desired cyclization of 17 to 19. Intrigued by this
divergence in reactivity, we attempted a coupling between pyrrole and carvone using the same
oxidant (18), and no product was observed (this was also the case using indole and carvone).
Although conceptually similar, the direct coupling of carbonyl compounds with pyroles (Figure
8) using a Cu\(^{II}\) oxidant probably differs mechanistically from the intramolecular cyclization (17
\(\rightarrow\) 19) using Fe\(^{III}\)-based 18. As shown in Figure 8, we believe that in the former case, an
intermediate Cu\(^{III}\)-chelated species (21) may be involved.\(^ {31}\) Reductive elimination and loss of
Cu\(^{1}\) should lead to 22 followed by tautomerization to product 23. Several observations support
this tentative mechanistic model: (1) dimerization of the pyrrole is never observed, as expected
based on geometrical constraints; (2) N-protected pyroles do not react; (3) only one equivalent
of oxidant is necessary, although 1.5 equiv gives a slight improvement in yield; and (4) the
characteristic reddish-brown color of copper(I)-salts is often observed at the end of the reaction.
The same trends are seen for the analogous coupling with indoles implying that a similar
mechanism may be active.\(^ {12}\) In contrast, to effect the conversion of 17 to 19, oxidant 18 was
employed since it had been firmly established by the scholarly studies of Jahn and co-workers to
convert enolates to radical species via an outer sphere single electron transfer pathway.\(^ {26}\)
Remarkably, just as the Fe\textsuperscript{III}-based oxidant 18 is ineffective for the couplings in Table 2, Cu\textsuperscript{II}-based oxidants are ineffective for the annulation (17 → 19). Alternatively, a mechanism can be conceived whereby the carbonyl radical adds into the pyrrole anion, generative the stabilized radical anion (24). Subsequent oxidation and tautomerization would result in formation of the product (23, Figure 8).

![Figure 8](image)

**Figure 8.** Proposed mechanism for the Cu\textsuperscript{II}-mediated coupling of pyrroles and carbonyl compounds.

### 6. Stephacidins

The heptacyclic alkaloid stephacidin A (34, Figure 10) poses a number of challenges for synthetic chemists. Naturally, our initial retrosynthetic analysis of 34 was influenced by literature precedent. For instance, pioneering work from the Williams lab\textsuperscript{32} has verified the proposals of Birch\textsuperscript{33} and Sammes\textsuperscript{34} that the bicyclo[2.2.2]diazaoctane core of these alkaloids is likely formed by a Diels–Alder reaction in Nature. However, this elegant biomimetic approach would be difficult to employ in an enantioselective laboratory synthesis of 34, especially since a proposed intermediate in the cascade sequence is achiral.\textsuperscript{35}

Our objective was to effect the conversion of 31 to 32, forging the key C–6 to C–22 bond (stephacidin numbering\textsuperscript{8}) with complete stereocontrol, using an oxidative coupling. In order to probe this key transformation, the model ester 25 (Figure 9) was synthesized and subjected to modified oxidative coupling conditions, which furnished the desired cyclized product 26 in 52% yield. The stereochemistry was secured upon removal of the MOM group, by X-ray crystallographic analysis of the resulting crystalline pentacycle 27 (See Figure 9 for ORTEP illustration).
Figure 9. Model studies for the oxidative coupling to form stephacidin (34).

With the encouraging reconnaissance gained in the model study, addition of LDA (2.2 equiv.) to a solution of substrate 31 in THF at –78 °C followed by Fe(acac)$_3$ after five minutes of enolization and warming to room temperature led to 32 in 61% yield as a single diastereomer. The extremely brief enolization time (five minutes) was essential for the success of this reaction.

The first total synthesis of the anti-cancer indole alkaloid, stephacidin A (34, Figure 10), and its conversion to avrainvillamide and stephacidin B has been accomplished by a concise route that features interesting chemistry and relies on the use of oxidative C–C bond formation. Among the highlights of the synthesis include a simple methodology for the gram-scale synthesis of substituted tryptophans, a method for thermal indole annulation, the first oxidative enolate coupling of an amide to an ester (Figures 9 and 10), and the first method for chemoselectively generating an unsaturated nitrone group, such as that found in avrainvillamide, from simple indole starting materials. The enolate coupling accomplishes the construction of two of stephacidin A’s three stereocenters with complete stereocontrol in a single operation. Finally, these syntheses secure the relative and absolute configuration of this natural product family and pave a potential path to the synthesis of analogs.
Figure 10. Short, enantioselective total synthesis of the stephacidsins and avrainvillamide.

7. Outlook and Conclusions

Oxidative enolate couplings have received very little attention in the chemical literature and have not previously, with the exception of the syntheses delineated above, been applied in the context of a complex total synthesis. While these recent successes in the arena of oxidative coupling proved to be very valuable for the construction of these complex natural products, it became abundantly clear throughout our study that very little is actually known about the process.

Several questions remain to be answered before this method will find widespread applicability as another tool in the synthetic chemist’s toolbox. For example, it remains to be determined what the mechanism of the transformation actually is. Additionally, much work remains to be done before a reliable and predictable model is elucidated that can enable the successful coupling of a myriad of different carbonyl species. Ideally, conditions need to be developed whereby any two carbonyl compounds can be selectively heterocoupled, based on the intrinsic reactivity of either the substrates on the oxidant.

Another question that may be posed is whether catalytic oxidative enolate couplings are in the horizon. While surprises undoubtedly remain for the future, it seems unlikely that such a
process could be made catalytic in an efficient manner. As the reaction stands, it is already a commercially viable process, in that it uses a very cheap oxidant (either Cu or Fe) as opposed to palladium or other transition metal catalysts. In fact, the oxidants used in the oxidative enolate couplings are the very re-oxidants used in many standard palladium reactions. Additionally, standard cheap re-oxidants for copper, such as oxygen, are incompatible with this reaction as they would likely oxidize the enolate species in preference to the metal.

As seen in our work involving hapalindoles, fischerindoles, ketorolac, avrainvillamide, and stephacidins, there are remarkable advantages to be gained in terms of **efficiency** (lack of protecting groups, halogens, disposable functional groups), *practicality* (extremely concise sequences), **stereoccontrol** (complete diastereoselectivity often observed), and **conservation of oxidation state** (oxidation state increases linearly in a synthesis by using innate functionality) when oxidative C–C bond formation is employed strategically.

### 8. Acknowledgements

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### 9. References:


